REMARKS/ARGUMENTS

An unmatched parenthesis has been deleted from claim 1. Applicants use the paragraph numbering of the office action in responding to the Examiner's comments.

1.4. Claims 1,15, 18, 22 and 132-134 stand rejected as obvious over Gurney, based on priority application 60/101,594 in view of common knowledge in molecular biology and Tang. Gurney is alleged to disclose the sequence of a protein later shown to be beta secretase. The Examiner acknowledges that Gurney et al. do not teach this sequence without residues 1-45 as claimed. Common knowledge is alleged to provide techniques for purifying a protein to homogeneity. Tang is cited as disclosing that aspartyl proteases have an N-terminal segment of about 45 residues that is cleaved off to produce a mature enzyme. The Examiner takes the view that it would have been obvious to combine the teachings of the references to provide a protein with potential clinical application with a success of 100% because truncation of a protein is routine. This rejection is respectfully traversed.

It is respectfully submitted that one would not have been motivated to combine Gurney with Tang with a reasonable expectation of success because one would not have known that Tang's comments regarding typical aspartyl proteases applied without modification to the unusual protein sequence reported by Gurney. Tang indicates that existing aspartyl proteases have a similar size of about 330 residues, and share important structural features such as positions of disulfide pairs (p. 55, first paragraph). However, the sequence reported by Gurney is unusual in many respects (see e.g., Dominguez et al., BACE1 and Presenilin: Two Unusual Aspartyl Proteases Involved In Alzheimer's Disease, Neurodegenerative Disease 1, 168-174 (2004); Haniu et al. Characterization of Alzheimer's β-Secretase Protein BACE: A Pepsin Family Member with Unusual Properties, JBC 275, 21099-21106 (2000)) (copies attached).[1] For example, the sequence has 501 amino acids not 330. The sequence is also reported by Gurney as having a transmembrane domain (albeit in the wrong place). None of the previously known

[1] With the recent amendment of the patent rules to include Rule 1.116(e), the consideration of additional evidence requires a showing of good and sufficient reasons why evidence is necessary and was not earlier presented. Here, the additional evidence addresses a new ground of rejection based on the Tang reference and could not have been presented earlier.

aspartyl proteases have such a domain. The sequence of Gurney also differs from known aspartyl proteases in the number of cysteine residues and hence the number of disulfide bonds that can be formed. Thus, Gurney's sequence is not a typical aspartyl protease.

Gurney's comments regarding cleavage of aspartyl proteases are made with regarding to previously known aspartyl proteases rather than his own sequence: "*Most* aspartyl proteases occur as a proenzyme whose N-terminus must be cleaved for activation" (at p. 5, first paragraph, emphasis supplied). Gurney does not speculate as to whether his own sequence shares the presence and same location of pro-domain as do most other aspartyl proteases. Given the substantial known differences between Gurney's sequence and existing aspartyl proteases in terms of amino acid length, transmembrane domain and cysteine, the artisan could not confidently conclude that the Gurney's sequences was similar to existing aspartyl proteases, in other respects, such as the presence and location of a pro domain.

The Examiner's comment that the artisan would have had a 100% expectation of success in producing a form of beta secretase lacking the first 45 residues and retaining beta secretase activity assume that the artisan would have known with complete certainty that the sequence of Gurney had a pro region and this ended at residue 45. In fact, however, the artisan did not know with certainty that Gurney's sequence had such a region. Although most aspartyl proteases, may have such a domain, Gurney's sequence is not a typical aspartyl protease. Further, if Gurney's protein did have such a region, the artisan would not know that it ended at residue 45. Given that the Gurney's sequence contains about 170 extra residues compared with other known proteases, the pro domain might have been thought to be substantially longer. Alternatively, due to the unique environment of Gurney's sequence as a transmembrane protein, the pro-domain might occur elsewhere in the protein than is typical of aspartyl proteases. In any event, it is unrealistic to think that the artisan would have a better understanding of the presence or location of such a domain than Gurney himself, who did not speculate on these matters in his own protein.

In view of the uncertainty regarding the presence and location of a pro domain in Gurney's sequence, it is respectfully submitted that the artisan would not have been impelled by the cited references to make a construct lacking the first 45 amino acids, nor would

he have a reasonable expectation of success that such a construct could be expressed to retain activity.

Applicants do not necessarily agree with the Examiner's other comments regarding the cited references. However, in view of the distinction drawn above, they are submitted to be moot and are not further addressed at this time.

Claims 23-25, 29-34 stand rejected as obvious over Gurney in view of common knowledge in molecular biology and Tang (all applied as above), in further view of Viswandhan, cited as teaching use of a crystalline composition to identify inhibitors. These claims are distinguished for at least the same reasons as claim 1.

1.5 Claim 1 stands rejected for obviousness type double patenting over claims 1, 2 and 6 of US 5,744,346. The Examiner says that patentability of a product depends on the product and not its methods of making from which the Examiner concludes that differences in the method of purification disclosed in the present application and the cited patent are not relevant. Applicants maintain traverse.

It is undisputed that the patentability of a product claim depends on the characteristics of the product itself and not its method of production. However, one of the characteristics of the present claims is that the claimed protein is "purified to apparent homogeneity." This element is a characteristic of the claimed product and must be taken into account in evaluating patentability. To establish a prima facie case the Examiner must provide reasons that obtaining apparent homogeneity from an isolated preparation of lesser purity would have been obvious.

Common general knowledge is not a sufficient reason to establish obviousness for the de novo isolation of a protein to apparent homogeneity from a natural source. Although purification of proteins from recombinant sources is often routine because such proteins can be expressed at high levels, and with tags to facilitate affinity purification, the same is not necessarily true for purification of proteins from natural sources. Many proteins of interest are expressed only at very low levels, and the purification process is empirical in nature, as was discussed in the last response. Beta-secretase in particular has proved elusive. There have been

a number of earlier reports purporting to purify this enzyme that are now recognized as having purified something else (see Pennisi, Science 286, 650 (1999) (copy attached))[2].

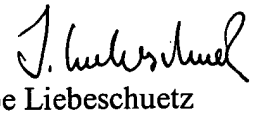
The present application's disclosure of a new method of purification was mentioned in the previous response because the previous office action took the position that the presents inventors had not disclosed such a new method (sentence bridging pp. 10-11 of office action). It is agreed that disclosure of a new method of production does not by itself prove that the resulting product is patentable. However, the existence of the new method is relevant to rebut any suggestion that common general knowledge must be enough to purify beta secretase to homogeneity because the present application discloses nothing else.

The burden of proof is on the Examiner to establish prima obviousness (in re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)). Merely citing to common general knowledge is not enough to fulfill the burden of proof that an elusive enzyme, such as beta secretase, could have been routinely be purified to homogeneity from a natural source.

The Examiner's citation of WO00/58479 is acknowledged. Applicants do not comment at this time on the Examiner's allegation that the application has a valid priority to March 26, 1999, except to point out that the present application has an earlier priority date.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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[2] The cited reference merely corroborates the factual positions presented earlier by applicants. The evidence was not presented earlier because applicants' believed the facts presented did not require corroboration. It is hoped that the issues in dispute will now be overcome or that the issues for appeal will be simplified after the Examiner has had an opportunity to review the reference.

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Attachments
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